Established vascular effects of continuous positive airway pressure therapy in patients with obstructive sleep apnoea-an update

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DOI: https://doi.org/10.3978/j.issn.2072-1439.2015.03.06

Review Article

Established vascular effects of continuous positive airway pressure therapy in patients with obstructive sleep apnoea—an update

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Abstract: The aim of this review was to summarize the current data from randomised controlled trials (RCTs) on vascular effects of continuous positive airway pressure (CPAP) therapy in patients with obstructive sleep apnoea (OSA). There is good evidence from RCTs that CPAP lowers blood pressure (BP) to a clinically significant amount. The effect seems to be dependent on the hours of nightly CPAP usage. Data from RCTs have also proven a beneficial effect of CPAP on measures of vascular function such as endothelial function and arterial stiffness. However, there is still a lack of evidence from RCTs proving that CPAP reduces vascular events and mortality.

Keywords: Obstructive sleep apoea (OSA); endothelial function; continuous positive airway pressure (CPAP); arterial hypertension

Submitted Oct 27, 2014. Accepted for publication Feb 04, 2015.
doi: 10.3978/j.issn.2072-1439.2015.03.06
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.03.06

Introduction

In the last thirty years a large body of observational and epidemiological studies has described an association between obstructive sleep apnoea (OSA) and increased incidence of vascular morbidity and mortality (1-4).

The findings of physiological studies and clinical trials have established that pathophysiological consequences of OSA such as sympathetic activity, intermittent hypoxia and oxidative stress as well as intrathoracic pressure swings play a key role in the development of vascular dysfunction in patients with OSA. Therefore a biological plausibility for a causal association between OSA and cardiovascular events can be assumed (5-7).

Continuous positive airway pressure (CPAP) is the gold standard therapy for OSA and has been proven to reduce daytime sleepiness and enhance quality of life in patients with OSA (8). Moreover, several observational studies suggested an association between CPAP therapy and reduced cardio- and cerebrovascular morbidity and mortality in patients with OSA. The mechanisms involved in this beneficial effect of CPAP on the vascular system likely include a reduction of blood pressure (BP) and improvement of vascular function (9-12).

The aim of this review was to summarize the currently established effects of CPAP on BP and vascular function in patients with OSA.

CPAP effects on BP

One major mechanism underpinning the association between OSA and cardiovascular disease is likely to be sustained arterial hypertension, and this association may possibly be enhanced by frequent nocturnal acute BP rises. The repetitive episodes of obstructive apnoeas and hypopnoeas are often associated with arousals and intermittent hypoxia, both of which lead to increased sympathetic nervous system activity and consequent considerable transient increases in arterial BP which can be as high as 80 mmHg. CPAP treatment has been shown to not only effectively abolish apnoeas, hypopnoeas and oxygen desaturations, but also to prevent arousals and, thus obviate acute BP rises (7,13).

Randomised controlled trials (RCTs) in patients with moderate to severe OSA

Several RCTs looking at the effect of CPAP on ambulatory BP have been conducted in the past decades; the results of these trials have established that CPAP treatment of patients with moderate to severe symptomatic OSA lowers BP to a variable extent. Most of the trials reported a reduction in BP of between 2 and 10 mmHg after several weeks of CPAP therapy (13,14). The effect of CPAP therapy on BP seems to depend on the severity of the sleep disordered breathing, the presence of daytime sleepiness, the extent of obesity, BP values before CPAP treatment and hours of nightly CPAP use (15-17). The findings of recent studies suggest that, in symptomatic patients, the beneficial effects of CPAP on BP are found mainly in those who show good adherence to treatment (e.g., at least 4 h per night), and this may also be true for patients without overt daytime sleepiness (18,19).

RCTs in patients with mild OSA

A common question faced by sleep physicians is at which level of disease severity patients with OSA should be treated. There is particular uncertainty about the need and the effectiveness of treatment in mild cases of OSA, especially when treatment would be prescribed to reduce cardiovascular risk.

Barnes *et al*. (20) performed a RCT in 28 patients with mild OSA [mean apnoea hypopnoea index (AHI) of 12.9/h], who underwent eight weeks of CPAP treatment *vs*. an oral placebo tablet. Compared to placebo, CPAP did not improve Epworth Sleepiness Scale (ESS) as a measure of daytime sleepiness. No benefit of CPAP compared to placebo was found on 24 h BP.

Newer data from a RCT conducted by Weaver *et al*. (21) evaluate the efficacy of CPAP treatment to improve functional status assessed by the Functional Outcomes of Sleep Questionnaire (FOSQ) in sleepy patients with mild and moderate OSA. A total of 239 patients with a mean AHI of about 13/h were randomized to CPAP treatment or placebo. After eight weeks CPAP treatment significantly improved the functional outcome of patients with mild OSA and there was a significant change in daytime diastolic BP values from baseline by –1.93 mmHg (95% CI, –3.8 to 0.0; P=0.048) between the two groups (21).

Both RCTs were not powered adequately to investigate the treatment effect on BP. Thus, further trials are needed to definitely clarify if patients with mild OSA benefit from CPAP treatment in terms of BP reduction.

RCTs in patients with oligo-symptomatic OSA

Half of all individuals with moderate to severe OSA do not report excessive sleepiness (22,23). An association between oligo-symptomatic OSA and cardiovascular disease has not been established so far, and it is unclear whether CPAP treatment results in improved vascular risk in this group of patients.

Recently, Barbé and colleagues (24) published the data of a RCT which evaluated the effect of CPAP treatment on the incidence of hypertension and cardiovascular events in a cohort of non-sleepy patients with OSA. The 725 consecutive patients with an AHI of ≥20/h and an ESS score of ≤10 were enrolled. In this cohort of OSA patients without daytime sleepiness, CPAP treatment did not result in a statistically significant reduction in the incidence of hypertension and cardiovascular events compared to usual care after a median follow-up of 4 years. However, there was some evidence that patients who were highly compliant with CPAP (>5.6 h/night) benefited from this treatment as a reduction of BP and cardiovascular events was observed in such patients (24).

In the Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular (MOSAIC) trial 391 patients with oligo-symptomatic OSA were randomised to 6 months of auto-adjusting CPAP therapy or standard care. The investigators demonstrated that CPAP treatment significantly improved subjective daytime sleepiness (adjusted treatment effect on ESS –2.0; 95% CI, –2.6 to –1.4; P<0.0001). However, this positive treatment effect on symptoms was not accompanied by a reduction in calculated vascular risk or BP (25).

The findings of the MOSAIC study were confirmed by a meta-analysis published by Bratton *et al*. (26), in which the individual data of 1,206 patients from four RCTs have been evaluated. Although CPAP treatment reduced OSA severity and sleepiness in minimally symptomatic patients, overall it did not to have a beneficial effect on BP, except in those patients who used CPAP for >4 h/night (26).

RCTs in patients with resistant hypertension

OSA has been proposed as a risk factor for resistant hypertension, which is defined as repeatedly measured BP >140/90 mmHg despite the use of three or more antihypertensive drugs of different classes. It has been estimated that more than 70% of patients with resistant hypertension have OSA (27).

There are a number of recently published RCTs on the effect of CPAP on BP in patients with resistant hypertension

(28-30). In a first RCT conducted by Lozano *et al*. (29), 64 patients were randomised to receive CPAP added to conventional treatment or conventional medical treatment alone. They completed a follow-up after 3 months and patients who used CPAP >5.8 h showed a greater reduction than patients treated with standard medication in daytime diastolic BP –6.12 mmHg (95% CI, –1.45 to –10.82; P=0.004), 24-h diastolic BP 6.98 mmHg (95% CI, –1.86 to –12.1; P=0.009) and 24-h systolic BP –9.71 mmHg (95% CI, –0.20 to –19.22; P=0.046). Additionally, the number of patients with a dipping pattern significantly increased in the CPAP group compared to conventional medical treatment (51.7% *vs*. 24.1%, P=0.008) (29).

Pedrosa *et al*. (28) randomised 20 patients with resistant hypertension to standard antihypertensive treatment and 20 patients to antihypertensive treatment plus CPAP for 6 months. Daytime ambulatory BP decreased significantly in the group allocated to antihypertensive treatment plus CPAP compared to standard antihypertensive treatment alone; the difference between groups in systolic and diastolic BP was also significant (9.6±6.6 and 6.6±4.6 mmHg; P<0.05). Interestingly, in this trial there was no beneficial effect of CPAP on nocturnal BP. This may be explained partly by recurrent arousals induced by the repetitive BP measurements during the night masking any underlying benefit, or the possibility that resistant hypertension is a hyperadrenergic condition that itself leads to frequent arousals (28).

In the HIPARCO-trial (30), a Spanish multicentre RCT, 194 patients with resistant hypertension and an AHI of ≥15/h were randomised to CPAP in addition to standard antihypertensive treatment or antihypertensive medication alone. After 12 weeks of CPAP treatment a higher prevalence of nocturnal dipper pattern and a reduction of nocturnal riser pattern have been observed. The recovery of the nocturnal dipper pattern may be advantageous for long-term cardiovascular outcome as the presence of a non-dipping or rising BP pattern is recognised as an independent cardiovascular risk factor (31). Linear regression analysis showed a reduction of 1.9 mmHg (95% CI, 0.6 to 3.3) in systolic BP and 1.0 mmHg (95 % CI, 0.1 to 1.8) in diastolic BP for each additional hour of CPAP use (30).

Meta-analyses

The extent to which CPAP can reduce BP in OSA patients is still under debate. Up to date, numerous meta-analyses evaluated the effects of CPAP on BP. In the following we focus on three recently published meta-analyses summarizing the relevant RCT data on the effect of CPAP therapy on BP (32-34).

Schein *et al*. (32) reviewed 16 RCTs which included 1,166 OSA patients in total. The use of CPAP resulted in clinically relevant reductions of BP; CPAP treatment was associated with a reduction of systolic BP by 3.20 mmHg (95% CI, 1.72 to 4.67) and diastolic BP by 2.87 mmHg (95% CI, 0.55 to 5.18) (32).

A further meta-analysis by Montesi *et al*. (34) including 32 RCTs showed similar results. OSA patients treated with CPAP benefitted from significant reductions in systolic BP by 2.58 mmHg (95% CI, 3.57 to 1.59) and diastolic BP by 2.01 mmHg (95% CI, 2.84 to 1.18). Night-time systolic BP was the variable with the most prominent reduction after treatment with CPAP (4.09 mmHg, 95% CI, 6.24 to 1.94) (34).

In their recently published meta-analysis of 29 RCTs including 1,820 participants, Fava *et al*. (33) also observed a decreased systolic BP (2.6±0.6 mmHg) and diastolic BP (2.0±0.4 mmHg) in patients with CPAP treatment. As a result of their meta-regression analysis they concluded that patients with frequent apnoeic episodes may experience the largest benefit from CPAP therapy with regard to BP reductions; for each increase in AHI of 10/h the systolic BP was predicted to decrease approximately 1 mmHg with CPAP treatment (33).

The relatively small treatment effects of CPAP on BP found in the meta-analyses may be related to methodological differences among the included trials, different study populations (e.g., sleepy and non-sleepy patients), sample sizes, study designs and the techniques used to measure BP (e.g., single time point, 24 h BP, beat-to-beat BP).

Clinical implications

Considering the recent RCT data, treatment with CPAP promotes small but clinically significant reductions in BP in individuals with OSA. Thus, a combined treatment including both antihypertensive medication and CPAP may be required in more severely hypertensive OSA patients. This combination is likely to be more effective in lowering both nocturnal and daytime BP than either treatment alone. The subsequent reduction in cardiovascular risk may be substantial, however this needs to be shown in a RCT (35,36).

CPAP effects on endothelial and vascular function

Endothelial dysfunction is an early marker of vascular

damage that precedes clinically overt vascular disease and is an important predictor of cardiovascular events. Early recognition of atherosclerotic changes and endothelial dysfunction may have an impact on risk stratification and thus influence the clinician's decision whether or not to aim for risk factor reduction in such patients. Evidence underpinning the association between OSA and impaired endothelial function and reduced endothelial repair capacity has been accumulating in recent years (37-41).

One well-described mechanism of endothelial dysfunction is the reduced bioavailability of endothelium-derived vasodilating factors such as nitric oxide (NO). Flow-mediated dilatation (FMD) of the brachial artery is currently the best-validated technique to non-invasively measure peripheral endothelial function. This method quantifies NO-mediated vasodilatation resulting from shear-stress mediated activation of endothelial NO synthase in response to an acute increase in luminal blood flow (42,43).

A possible underlying mechanism for endothelial dysfunction in patients with OSA seems to be a down regulation of endothelial NO synthase as a result of increased sympathetic activity, oxidative stress, excessive arterial wall shear stress caused by recurrent surges in BP during apnoeic events, increased endothelial cell apoptosis as well as increased levels of coagulation factors and cholesterol (37,44).

RCTs in patients with moderate to severe OSA

The first RCT investigating the impact of CPAP therapy on FMD in moderate to severe OSA by Ip and colleagues (45) resulted in a significant increase of FMD in the CPAP group after four weeks of therapy, whereas those on standard care showed no significant change (absolute between-group difference in FMD of 5.4%, P<0.001).

In a RCT conducted by Kohler *et al.* (18) a significant decrease in endothelial function (FMD) was observed after 1 week [–1.7% (95% CI, –2.8 to –0.6); P<0.002] and 2 weeks [–3.2% (95% CI, –4.5 to –1.9); P<0.001] of CPAP withdrawal in patients with moderate-severe OSA compared to continued CPAP use.

RCTs in patients with mild OSA

To date, there are no published data from RCTs on the effect of CPAP on endothelial function in patients with mild OSA.

RCTs in patients with oligo-symptomatic OSA

Recent data from the MOSAIC-trial, a multicentre RCT evaluating the cardiovascular risk in 391 patients with minimally symptomatic OSA, CPAP treatment showed beneficial effects on endothelial function as assessed by FMD +2.1% (95% CI, 1.0 to 3.2; P<0.001). The improvement in FMD was larger in patients using CPAP for >4 h/night than in those who used it less (P<0.013) (46).

Meta-analysis

Between 2004 and 2013, 6 RCTs have been performed measuring FMD in patients with OSA before and after 2-24 weeks of CPAP treatment. RCTs evidenced that CPAP treatment improves endothelial function. Compared to the control group, CPAP therapy significantly increased FMD by 3.9% (95% CI, 1.9 to 5.8, P<0.0001) (47).

CPAP effects on arterial stiffness

Increased arterial stiffness is an early indicator of arterial disease. Augmentation index (Aix) and pulse wave velocity (PWV) are measures of arterial stiffness and independently predict cardiovascular events in high-risk populations (48). The shape of the pressure waveform of an artery provides a measure of arterial stiffness and can be assessed by the technique of pulse wave analysis (49).

RCTs in patients with moderate to severe OSA

Drager *et al.* (50) randomly assigned 24 patients with severe OSA without comorbidities to receive no treatment or CPAP for 4 months. After this period of CPAP treatment they found a significant decrease of arterial stiffness as assessed by PWV (10.4±1.0 *vs.* 9.3±0.9 m/s; P<0.001) (50).

In another RCT by Kohler *et al.* (14) a significantly decreased Aix from 14.5% to 9.1% was observed in patients with moderate to severe OSA after 4 weeks of CPAP treatment compared to sham CPAP. This considerable reduction is comparable in size to the effect seen after 12 weeks of exercise training in patients with coronary artery disease or after 6 weeks of eprosartan (600 mg daily) in patients with never treated arterial hypertension (14).

In contrast, Jones *et al.* (51) could not find a significant decrease of Aix (15.5%±11.9% *vs.* 16.6%±11.7%; P=0.08) in 43 patients with an AHI >15/h after 12 weeks of CPAP or sham-CPAP treatment in their RCT. An important limitation of this study and possibly the reason why there was no significant effect of CPAP on Aix in the latter study is the very low nightly CPAP usage of 3 h/night (51).

RCTs in patients with mild OSA

At present there are no data from RCTs evaluating the effects of CPAP therapy on arterial stiffness in patients with mild OSA.

RCTs in patients with oligo-symptomatic OSA

A recently published RCT assessed Aix by pulse wave analysis in 208 non-sleepy OSA patients who underwent 6 months of CPAP treatment or continued standard care. There was no statistically significant effect of CPAP on Aix observed (–1.4%; 95% CI –3.6 to 0.9; P<0.23). An explanation for the lack of an effect in this study may be that the population of patients were not only non-sleepy but also had milder OSA than in the other published RCTs (50,52). In addition, the study population had a higher age and higher proportion of patients with cardiovascular comorbidities than those of previous studies, both of which are well known to increase arterial stiffness and, thus, may have masked a positive effect of CPAP (46).

Meta-analysis

A recently published meta-analysis by Vlachantoni *et al*. (48) included 615 patients from 11 interventional studies and four RCTs. Overall significant improvements were observed in all indices of arterial stiffness after CPAP treatment.

Nevertheless, the potential beneficial effects of CPAP in reducing arterial stiffness in patients with mild OSA and the impact of CPAP adherence on the treatment effect should be explored in future studies (48).

CPAP effects on vascular events

Data from observational cohort studies suggest that OSA is associated with vascular morbidity and mortality (1,12). In contrast to these findings, Barbe and colleagues (24) as well as the investigators of the MOSAIC-trial (25), who analysed the effects of long-term CPAP therapy on cardiovascular risk in non-sleepy OSA patients could not establish a beneficial effect of CPAP treatment on cardiovascular events.

Thus evidence is needed from large RCTs to evaluate whether CPAP treatment is a useful therapy to prevent vascular events in patients with OSA. There is ongoing research in this field and data answering some of the open questions may soon be available (53).

Promising is the Sleep Apnea Cardiovascular Endpoints Study SAVE (NCT00733343), a multi-centre, open label, parallel, prospective, RCT that investigates the effects of CPAP treatment plus standard care versus standard care alone in 2,500 high risk subjects for CAD with moderate-severe OSA. The trial will determine the effects of CPAP treatment over a 2-7-year follow-up period on new cardiovascular events, including MI, stroke and cardiovascular death. The study is conducted in China, Australia, New Zealand, Spain and Brazil and a completion of this trial is announced for December 2015 (5,54).

Another large-scale multi-centre RCT (the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea-RICCADSA trial, NCT0051959) investigates patients with asymptomatic OSA and stable CAD. This study completed recruitment and included 511 patients with CAD undergoing planned percutaneous or surgical coronary revascularization and assesses whether CPAP treatment reduces the combined rate of new revascularization, MI, stroke and cardiovascular mortality over a follow-up period of 3 years (55).

ISAACC, another notable trial (CPAP in Patients With Acute Coronary Syndrome and OSA-trial, NCT 01335087) will include more than 1,800 OSA patients with a recent acute coronary syndrome (ACS) to clarify whether CPAP treatment reduces the rate of major cardiovascular events in patients with non-ST elevation or ST elevation ACS admitted to a coronary care unit during a 12-month follow-up (53,56).

The US National Institute of Health has funded three planning grants, the Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT, NCT01086800), Best Apnea Interventions in Research (BestAIR, NCT01261390) and the Sleep Apnea in TIA/Stroke (SleepTight, NCT01446913) studies to evaluate design approaches for a large scale clinical trial of CPAP for cardiovascular risk reduction, including effectiveness of various recruitment strategies, methods for optimizing adherence, use of control treatments, intermediate endpoints most responsive to intervention and the use of oxygen as an alternative to CPAP (5).

Conclusions

Although numerous RCTs found clinically significant reductions of BP with CPAP treatment in patients with moderate to severe symptomatic OSA, CPAP indication is still debatable in patients with mild OSA or in patients without daytime sleepiness. Hence, OSA treatment must be tailored for each patient, based on metabolic and

cardiovascular risks and the willingness of patients to use CPAP on a nightly basis. Alternative or combined treatments are needed to reduce cardiovascular risk, particularly in minimally symptomatic patients, who are less likely to accept CPAP (57). The ongoing RCTs have to be awaited before CPAP therapy can be regarded as an effective treatment to protect from vascular morbidity and mortality (37).

Acknowledgements

Funding: This work was supported by Swiss National Science Foundation Grant number 32003B-143365/1 and the Clinical Research Priority Program Sleep and Health at the University of Zurich, Switzerland.
Disclosure: The authors declared no conflicts of interest.

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Cite this article as: Wons AM, Kohler M. Established vascular effects of continuous positive airway pressure therapy in patients with obstructive sleep apnoea—an update. J Thorac Dis 2015;7(5):912-919. doi: 10.3978/j.issn.2072-1439.2015.03.06

